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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,059	12/14/2005	William Marshall Stark	056646-5024	2559

9629 7590 07/10/2008
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EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	
ART UNIT	PAPER NUMBER
1652	
MAIL DATE	DELIVERY MODE
07/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,059	STARK ET AL.	
	Examiner	Art Unit	
	IQBAL H. CHOWDHURY	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 March 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-10,12-14,18-23,28-42,46,47,52-59,67 and 68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *3 and 4* is/are allowed.

6)☒ Claim(s) *1-2,7-10,12-14,18-23,28-42,46,47,52-59,67 and 68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-4, 7-10, 12-14, 18-23, 28-42, 46-47, 52-59 and 67-68 are currently pending.

In response to a previous Office action, a non-final action (mailed on October 19, 2007), Applicants filed a response and amendment received on March 19, 2008, amending claims 1-4, 7-10, 12-14, 18-23, 28-42, 46-47 and 52-59, and cancelling claims 5-6, 11, 15-17, 24-27, 43-45, 48-51, and 60-66 is acknowledged.

Claims 1-4, 7-10, 12-14, 18-23, 28-42, 46-47, 52-59 and 67-68 are under consideration and are present for examination.

Applicants' arguments filed on March 19, 2008, have been fully considered but are not deemed persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Withdrawn-Drawings objection

Previous objection of drawings submitted on 3/24/2005 is withdrawn in view of applicants' amendment of drawings legend with addition of SEQ ID NOs for corresponding sequences.

New-Claim Objections

Claim 7 is objected to in the recitation "M103I or at positions" should be "M103I at positions". Appropriate correction is required.

Claims 13, 57 and 58 are objected to in the recitation "or the position" should be "at the position". Appropriate correction is required.

Claim 53 is objected to in the recitation "further comprising a one or more mutations" should be "further comprising one or more mutations". Appropriate correction is required.

Claim 39 is objected to in the recitation "M103I and Q105L" should be "M103I, Q105L". Appropriate correction is required.

Withdrawn-Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Previous rejection of Claims 8-10 and 53-56 under 35 U.S.C. 112, second paragraph, as being indefinite in the recitation of "1,3 or 1,2 or 2,3 interface" is withdrawn in view of applicants persuasive arguments. Indeed, the specification at page 3 discloses interface 1,2 and 2,3 and amino acid residues forming 1,2 interface are disclosed at page 46, Table 1 on page 61, and amino acid residues of 2,3 interface are disclosed at page 49 and in Fig. 4.

New-Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-2, 7-10, 12-14, 28-42, 46-47, 52-59 and 67-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1, 28, 46 recite "one or more additional mutation --------- L105 ----- of TN3 resolvase (SEQ ID NO: 2", which is unclear to the Examiner. TN3 resolvase of SEQ ID NO: 2, does not have any leucine (L) at position 105 but

rather glutamine (Q). Accordingly, claims 2, 7-10, 12-14, 29-42, 47, 52-59 and 67-68 are also rejected as they depend on claims 1, 28 or 46.

Claims 12-13, are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 12 recites "according to claim 1 further comprising the mutations ----- G101S, which is unclear to the Examiner because claim 1 already recites a polypeptide having a mutation at position G101. How polypeptides have a further mutation at a position, which is already mutated?

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 21 is indefinite in the recitation "according to claim 18 wherein the Zif268 DNA binding domain" lacks antecedent basis and claim 18 does not recite anything about "Zif268 DNA binding domain". This rejection can be overcome by depending from claim 19.

Claim 28 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 28 is indefinite in the recitation "according to claim 18 wherein said catalytic domain comprises one or more additional mutation, which is confusing because claim 18 does not include any mutation.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Previous rejection of Claims 1-2, 7-10, 12-14, 18-22, 28-42, 46-47, 52, 57-59 and 67-68 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. This rejection has been discussed at length in the previous office action. The rejection is maintained for the following reasons.

Claims 1-2, 7-10, 12-14, 18-22, 28-42, 46-47, 52, 57-59 and 67-68 are directed to a genus of a serine recombinase comprising a catalytic domain and a DNA binding domain, wherein said catalytic domain is mutated at G101 or at a position corresponding to G101 of TN3 resolvase of SEQ ID NO: 2, wherein said serine recombinase comprising any one or more additional mutations at a position selected from the group consisting of L105, V107, A117, A89, F92, L66, G70, M76, T109, and R121 or one or more additional mutations at said positions corresponding to TN3 resolvase of SEQ ID NO: 2 or any hybrid recombinase comprising a catalytic domain from a serine recombinase, and a DNA binding domain of any Zif268 protein, wherein said hybrid recombinase is capable of binding nucleic acid by said DNA binding domain and catalyzing recombination of said DNA or any catalytic domain of a serine recombinase which has been mutated at G101 or at a position corresponding to G101 of a Tn3 resolvase of SEQ ID NO: 2 and a kit comprising any serine recombinase or any hybrid recombinase.

Applicants argue that the specification provides extensive guidance of the structural features (both secondary and tertiary) of serine recombinases which are important for the present invention, wherein these features are described with reference to both Tn3 resolvase and γ/δ resolvase. Applicants also argue that the serine recombinase family of related enzymes is well known in the art and, as described on page 12 of the specification, members of this protein

family share significant sequence identity and Figure 1 displays an alignment of fourteen (14) separate and distinct serine recombinases, and indicates that a number of residues are conserved across different members of this protein family.

This is not found persuasive because none of these features are present in the claims, i.e. the claimed serine recombinase does not have to have these characteristics. Besides, serine recombinases are a large family of recombinases, use a catalytic serine for strand cleavage, recognize shorter attP sequences, and do not require host cofactors, which is substantially different from tyrosine recombinases (Groth et al. 2004). Besides, Tn3 and γ/δ resolvase, the known other serine recombinases are Phage integrase, QC31, R4, TO901 and gin (phage Mu), which are functionally similar to Tn3 and γ/δ resolvase but structurally different, which suggests that functions could be provided by other unrelated structures.

Applicants further argue that it is expected that the effects observed from mutation of the Tn3 resolvase may also be expected in other members of the serine recombinase protein family. For example, mutation of the corresponding residues in a Sin recombinase from *Staphylococcus aureus,* which is functionally quite distant from Tn3 resolvase, produces entirely predictable results. Such results are discussed on page 13 of the specification beginning at line 20.

Applicant's arguments and amendments to claims have been fully considered but are not deemed persuasive to overcome the rejection on written description issues.

Examiner acknowledges amendments to the claims (some additional mutations and SEQ ID NO: 2 for TN3 resolvase), however the amendment does not give enough structural feature of a serine recombinase having any one or more additional mutations of said positions recited in claims 1, 7, 10, 12, a catalytic domain and a DNA binding domain, wherein said catalytic

domain is mutated at G101 or at a position corresponding to G101 of TN3 resolvase of SEQ ID NO: 2, wherein said serine recombinase comprising any one or more additional mutations at a position selected from the group consisting of L105, V107, A117, A89, F92, L66, G70, M76, T109, and R121 or one or more additional mutations at said positions corresponding to TN3 resolvase of SEQ ID NO: 2 or any hybrid recombinase comprising a catalytic domain from any serine recombinase, and DNA binding domain of any Zif268 protein, wherein said hybrid recombinase is capable of binding nucleic acid by said DNA binding domain and catalyzing recombination of said DNA or any catalytic domain of any serine recombinase which has been mutated at G101 or at a position corresponding to G101 of a Tn3 resolvase of SEQ ID NO: 2 and a kit comprising any serine recombinase or any hybrid recombinase, i.e. the recitation of "one or more additional mutations", which interprets unlimited number of mutations that makes the protein having no structural feature. An ordinary skilled in the art will not be able to practice the claimed invention without having a specific structural feature, i.e. structure and function correlation, which is required for fulfilling written description requirements. Contrary to applicants arguments, claims still read on any one or more additional mutations of said serine recombinase comprising any catalytic domain corresponding to positions of SEQ ID NO: 2. The Examiner acknowledges that specification provide some species as well as guidance such as sequence alignment data but those information are not correlated with the claims as written. As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional

characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. Satisfactory disclosure of a representative number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of species disclosed. For inventions in an unpredictable art, adequate written description of a genus, which embraces widely variant species, cannot be achieved by disclosing only one species within the genus. The specification teaches few representative species of SEQ ID NO: 2 and few modifications. The genus of polypeptide of a serine recombinase is structurally diverse as it broadly encompasses many variants comprising recombinase activity having different structures. Therefore, disclosing similar modifications would not be sufficient to describe the claimed invention, which also encompasses many other mutations at the same time nor are the claims limited to making the mutations in serine recombinases having the specific characteristics, i.e. having common identity of amino acid residues among different serine recombinases or serine recombinases known in the art nor are the mutant enzymes that are made required to have these characteristics. As such, the disclosure solely of functional features coupled with minor structural feature, present in all members of the genus is insufficient to be representative of the attributes and features of the entire genus. Therefore, the rejection is maintained.

Since, the disclosure in particular Fig. 1 provide an evidence of substantial homology of serine recombinases (species) with TN3 resolvase (SEQ ID NO: 2), the rejection can be overcome by adding the limitation such as "a consensus sequence" among the claimed serine recombinases, which is 95% identical to SEQ ID NO: 2 (provided that the specification has the support) or one or more addition, deletion or substitution more preferably 1-10 or 1-20 amino acid residues in a particular domain corresponding to SEQ ID NO: 2.

Previous rejection of Claims 1-2, 7-10, 12-14, 18-22, 28-42, 46-47, 52, 57-59 and 67-68 under 35 U.S.C. 112, first paragraph on scope of enablement is maintained. This rejection has been discussed at length in the previous office action. The rejection is maintained for the following reasons.

The specification, while being enabling for a serine recombinase Tn3 resolvase of SEQ ID NO: 2 from E. coli comprising a catalytic domain and a DNA binding domain, wherein said catalytic domain is mutated at G101 or at a position corresponding to G101 of Tn3 resolvase of SEQ ID NO: 2, wherein said serine recombinase contains one or more additional mutations all at positions selected from the group consisting of L105, V107, A117, A89, F92, L66, G70, M76, T109, and R121 or at said positions corresponding to TN3 resolvase of SEQ ID NO: 2 or a hybrid recombinase comprising a catalytic domain of Tn3 resolvase of SEQ ID NO: 2, and a DNA binding domain of a Zif268 protein, wherein said hybrid recombinase is capable of binding nucleic acid by said DNA binding domain and catalyzing recombination of said DNA or a catalytic domain of a serine recombinase of Tn3 resolvase of SEQ ID NO: 2, which has been mutated at G101 corresponding to G101 of a Tn3 resolvase of SEQ ID NO: 2 and a kit

comprising said serine recombinase of Tn3 resolvase of SEQ ID NO: 2 or a hybrid recombinase, does not reasonably provide enablement for a serine recombinase having a mutation G101S and any number of additional mutations including a mutation at the recited positions comprising any catalytic domain and any DNA binding domain, wherein said catalytic domain is mutated at G101 or at a position corresponding to G101 of a Tn3 resolvase of SEQ ID NO: 2 or a hybrid recombinase comprising any catalytic domain and any DNA binding domain, wherein said hybrid recombinase is capable of binding nucleic acid by said DNA binding domain and catalyzing recombination of said DNA or any catalytic domain of a serine recombinase having any one or more additional mutations and a kit comprising said serine recombinase or a hybrid recombinase comprising said serine recombinase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants argue that those residues tolerant to modification are specified in the amended claims, and the specification clearly describe these residues with reference to the amino acid sequence of Tn3 resolvase and also with reference to structural characteristics such as their position at the 1,2 interface (see, for example, Figure 6).

This is not found persuasive because claims are not limited to only this.

Applicants also argue that high resolution crystal structures have been obtained for several members of the serine recombinase family, and these may be used in conjunction with biochemical structural data to enable the skilled artisan to easily identify the residues in other

serine recombinases that correspond to the Tn3 residues which, when mutated, cause hyperactivity.

This is not found persuasive because the problem is not the ability to identify the residues corresponding to those mutated in the instant specification in other related serine recombinases but the lack of limitation on the number of mutations, which can be present.

Applicants submit that the specification does disclose sufficient information to enable the skilled artisan to practice the claimed invention using any catalytic domain and any DNA binding domain of any serine recombinase. Further, the specification discloses significant guidance of the features necessary for a heterologous DNA binding domain which make it applicable to the hybrid recombinases of the present invention (see, for example, pages 18 to 21 of the specification).

Applicants arguments have been fully considered but are not deemed persuasive to overcome the rejection on scope of enablement issues. The Examiner acknowledges the amendment to the claims and the arguments that the specification discloses sufficient number of mutations with regard to TN3 resolvase and amino acid residues at 1,2 and 2,3 interfaces and known crystal structures, which causes the enzyme hyperactive but disagrees with the applicants contention that the claimed invention is enabled for full scope claimed because applicants are claiming any serine recombinase having a mutation of G101 and any one or more additional mutations at recited positions corresponding to TN3 resolvase of SEQ ID NO: 2. Since, serine recombinases are diverse which encompass many mutations as well as hybrid recombinase; one

of ordinary skilled in the art would not know how to make the claimed mutant protein from the guidance of TN3 resolvase of SEQ ID NO: 2, which require undue experimentation.

Claims 1-2, 7-10, 12-14, 18-22, 28-42, 46-47, 52, 57-59 and 67-68 are substantial broad in the context of the recitation "one or more additional mutations at recited positions corresponding to TN3 resolvase of SEQ ID NO: 2. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the substantially large number of serine recombinases broadly encompassed by the claims.

Claims 1, 7-10, 12-14, 18-23, 28-42, 46-47, 52, 57-59, 67-68 are broadly drawn to a serine recombinase comprising any catalytic domain, wherein said serine recombinase comprises any one or more additional mutations at said positions corresponding to TN3 resolvase of SEQ ID NO: 2. Claims do not specify any specific sequence due to the recitation of "one or more additional mutations, which lacks structural feature. The specification is enabled for serine recombinase of SEQ ID NO: 2 with a mutation at position G101 and corresponding several mutations as well as hybrid recombinase comprising catalytic domain of SEQ ID NO: 2 and a kit comprising serine recombinase of SEQ ID NO: 2. The claims broadly encompass a serine recombinase with one or more amino acid substitutions recited in the claims and do not limit the claims to SEQ ID NO: 2 only. Also, while the specification may provide some guidance as to which amino acids can be mutated to obtain the desired functional properties if there is a significant level of homology between related serine recombinases, in the instant case, it is unclear as to how the teachings of the specification adequately enabled the mutation of a serine recombinase having one or more additional mutations having claimed functional characteristics.

While as discussed by the applicants the specification provides some guidance with

regard to serine recombinases, the guidance provided substantial amount of guidance but the specification lacks the guidance for enable the full scope of the claims.

As discussed previously, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a serine recombinase comprising a mutation at position G101 and any one or more additional mutations at said positions corresponding to SEQ ID NO: 2 comprising any catalytic domain and any DNA binding domain, wherein said catalytic domain is mutated at G101 or at a position corresponding to G101 of a Tn3 resolvase of SEQ ID NO: 2 or a hybrid recombinase comprising any catalytic domain and any DNA binding domain, wherein said hybrid recombinase is capable of binding nucleic acid by said DNA binding domain and catalyzing recombination of said DNA or any catalytic domain of said serine recombinase and a kit comprising any serine recombinase or a hybrid recombinase comprising any serine recombinase. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of a modified serine recombinase having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Therefore, the rejection is maintained.

Withdrawn-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the

basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Previous rejection of Claims 1-2, 7-8, 10, 14, 46-47, 52-53, 55-56, and 59 under 35 U.S.C. 102(b) as being anticipated by Arnold et al. (Mutants of Tn3 resolvase which do not require accessory binding sites for recombination activity, EMBO J. 1999 Mar 1; 18(5): 1407-14, see IDS) is withdrawn in view of applicants amendment of claims 1, 10 and 46. Indeed, Arnold et al. do not teach one or more additional mutations recited in said claims.

Previous rejections of Claims 1-4, 7-10, 12, 14, 46-47 and 52-59 under 35 U.S.C. 102(b) as being anticipated by Sarkis et al. (A model for the gamma delta resolvase synaptic complex, Mol Cell. 2001 Sep;8(3): 623-31, see IDS) is withdrawn in view of applicants amendment of claims 1, 10 and 46. Indeed, Sarkis et al. do not teach one or more additional mutations recited in said claims.

Maintained-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Previous rejection of Claims 18-23, 28-35, 38-39, 41-42, 57 and 68 under 35 U.S.C. 103(a) as being unpatentable over Arnold et al. (Mutants of Tn3 resolvase which do not require accessory binding sites for recombination activity, EMBO J. 1999 Mar 1; 18(5): 1407-14), Sarkis et al. (A model for the gamma delta resolvase synaptic complex, Mol Cell. 2001 Sep;8(3): 623-31, in view of Jamieson et al. (A zinc finger directory for high-affinity DNA recognition. Proc Natl Acad Sci U S A. 1996 Nov 12; 93(23): 12834-9) is maintained. Instant claims are directed to a hybrid or chimeric recombinase i.e. Tn3 resolvase, wherein the catalytic domain is from Tn3 resolvase of E. coli and a heterologous DNA binding domain of Zif268 and a linker sequence comprises SEQ ID NO: 31 and a kit comprising said hybrid recombinase.

Arnold et al. teach a mutant serine recombinase Tn3 resolvase comprising a mutation at position G101, wherein the mutation is G101S. Arnold et al. also teach additional mutations including E124Q, D102Y, M103I, which are located on the surface of the interface of a serine recombinase. Since, applicants define mutation at position E124 in the specification, which is at 1,2 interface of a serine recombinase, mutation at position E124 as E124Q as taught by Arnold et al. would inherently be in the 1,2 interface of a serine recombinase. Arnold et al. further teach a catalytic domain of a serine recombinase comprising a mutation of G101S, and further comprising additional mutations including E124Q, D102Y, wherein catalytic domain also

comprises an interface including mutation of at positions M 103I. The catalytic domain of Arnold et al. and the instant application is the same. Therefore, the length (amino acid 1-148) of the catalytic domain (claims 31-35) of Arnold et al. would be the same as the instant application. Sarkis et al. teach a catalytic domain having all the mutations of claim 57. Arnold et al. do not teach a hybrid or chimeric or recombinant recombinase of Tn3 resolvase having a heterologous DNA binding domain, a linker sequence and a kit comprising said hybrid recombinase.

Sarkis et al. teach a mutant serine recombinase Tn3 resolvase comprising a mutation at position G101, wherein the mutation is G101S a mutant serine recombinase Tn3 resolvase, and further comprising a mutation Q105L, having one or more mutations at the 2,3 interface R2A and E56K. Sarkis et al. also teach catalytic domain of a serine recombinase comprising a mutation of G101S, and further comprising additional mutations including E124Q, D102Y, wherein catalytic domain also comprises an 2,3 interface including mutation at position M 103I and DNA binding domain. The catalytic domain of Sarkis et al. and the instant application is the same. Therefore, the length (amino acid 1-148) of the catalytic domain (claims 31-35) of Sarkis et al. would be the same as the instant application. Sarkis et al. teach a catalytic domain having all the mutations of claim 57. Sarkis et al. do not teach a hybrid or chimeric or recombinant recombinase of Tn3 resolvase having a heterologous DNA binding domain or a linker sequence and a kit comprising said hybrid recombinase.

Jamieson et al. teach a DNA binding domain Zif268, a murine transcription factor egr-1 family, which is a Zinc finger DNA binding domain having the ability to bind DNA molecule comprising G-rich region.

By combining the teachings of Arnold et al., Sarkis et al., and Jamieson et al. it would have been obvious to one of ordinary skill in the art at the time of the invention was made to replace the DNA binding domain of Tn3 resolvase of Arnold et al. and Sarkis et al. with DNA binding domain of Jamieson et al. to make a hybrid or chimeric or recombinant recombinase because the DNA binding domain of Jamieson et al. has the affinity to bind G-rich region of a DNA sequence in order to direct the recombinase activity to a desired new site. Since, DNA binding domain are present in both transcription factors and recombinase, both of which need to bind specific DNA sequence for exerting their functional activities by catalytic domain of recombinase for excising DNA and recombination, or recruiting RNA polymerase for the activation of transcription. One of ordinary skill in the art would be expected to make a kit comprising said hybrid recombinase for convenience for the user. It would have been obvious to one of ordinary skill in the art to insert a linker between catalytic domain of Arnold et al. and Sarkis et al. and DNA binding domain of Jamieson et al. to make a recombinant protein, which is widely used in the art to make the recombinant protein express efficiently and function properly.

One of ordinary skill in the art would have been motivated to use Zif268 DNA binding domain instead of Tn3 resolvase DNA binding domain for specifically recombination of G-rich region.

One of ordinary skill in the art would have a reasonable expectation of success because making a hybrid or chimeric or recombinant protein is well known in the art.

Therefore, claims 18-23, 28-35, 38-39, 41-42, 57 and 68 would have been prima *facie* obvious to use one of ordinary skill in the art.

Applicants argue that same claims (18-22, 38-39, 41-42) are also rejected for lack of enablement under 35 U.S.C. 112 (first paragraph) and to establish *a prima facie* conclusion of obviousness, the Examiner must combine prior art elements according to known methods to yield predictable results (see M.P.E.P. 2143). Applicants also argue that according to Examiner, it is not routine in the art to screen for multiple substitutions as encompassed by the instant claims and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity are limited in any protein and the result of such modifications is unpredictable, and it is therefore unclear to Applicants how the Examiner can maintain that these claims are obvious while the same claims are not enabled by the specification. Clearly the Examiner is picking a chosen embodiment of the claims to support these rejections and not considering the claims as a whole. Applicants therefore submit that the Examiner has not established a *prima facie* case of obviousness in his rejection of the claims.

This is not found persuasive because the core issue for lack of enablement for full scope of the claim is due to unlimited number of mutations of a serine recombinase due to any one or more additional mutations at said position corresponding to the positions of SEQ ID NO: 2, which is enormously broad and the scope of the claim is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of serine recombinase broadly encompassed by the claims. Although, the specification provides substantial amount of guidance but such guidance is not sufficient to enable full scope of the claim. However, the 103 rejection was based on the substituting serine recombinase DNA-binding domain with heterologous DNA-binding domain, which means that two issues are different. One of ordinary

skilled in the art would be motivated to substitute DNA binding domain of serine recombinase with a DNA-binding domain of Jamieson et al. since, said DNA-binding domain is function in terms DNA-binding ability. By combining the teachings of Arnold et al., Sarkis et al., and Jamieson et al. it would have been obvious to one of ordinary skill in the art to arrive the claimed invention because Arnold et al. and Sarkis et al. teach the claimed invention except the DNA binding domain in the hybrid recombinase, wherein said heterologous DNA-binding domain is taught by Jamieson et al. Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention was made to replace the DNA binding domain of Tn3 resolvase of Arnold et al. and Sarkis et al. with DNA binding domain of Jamieson et al. to make a hybrid or chimeric or recombinant recombinase because the DNA binding domain of Jamieson et al. has the affinity to bind G-rich region of a DNA sequence in order to direct the recombinase activity to a desired new site. Since, DNA binding domain are present in both transcription factors and recombinase, both of which need to bind specific DNA sequence for exerting their functional activities by catalytic domain of recombinase for excising DNA and recombination, or recruiting RNA polymerase for the activation of transcription. One of ordinary skill in the art would be expected to make a kit comprising said hybrid recombinase for convenience for the user. It would have been obvious to one of ordinary skill in the art to insert a linker between catalytic domain of Arnold et al. and Sarkis et al. and DNA binding domain of Jamieson et al. to make a recombinant protein, which is widely used in the art to make the recombinant protein express efficiently and function properly.

Besides, **Supreme Court** decision on *KSR Int'l v. Teleflex, Inc.* further strengthen the TSM test (teaching, suggestion and motivation) to combine the prior art elements to meet the

claimed subject matter (see KSR Int'l Co. V. Teleflex, Inc., No 04-1350, US Apr. 30, 2007). Therefore, the rejection is maintained as discussed. The cited references teach all the limitation of claimed invention and one of ordinary skill in the art would be motivated to combine the teachings of the references to arrive the claimed invention (see KSR Int'l Co. V. Teleflex, Inc., No 04-1350, US Apr. 30, 2007).

Conclusion

Status of the claims:

Claims 1-4, 7-10, 12-14, 18-23, 28-42, 46-47, 52-59 and 67-68 are pending.

Claims 3 and 4 are allowed.

Claims 1-2, 7-10, 12-14, 18-23, 28-42, 46-47, 52-59 and 67-68 are rejected.

No claims are allowed.

Applicants must respond to the objections/rejections in each of the sections in this Office action to be fully responsive in prosecution. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P., 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R., 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R., 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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